REMARKS

The Final Office Action dated 3/25/2004 rejected claims 1-4, 7-9 and 12. Claims 30 and 31 were with drawn from consideration pursuant to an earlier restriction requirement and are now canceled without prejudice for purposes of allowance of remaining claims. Claims 13 and 20 were previously allowed. Previously, claims 6, 10, 11, 17, 19, 21 and 23-29 were canceled without prejudice by Preliminary Amendment dated 12-14-2001.

By this Amendment, all remaining claims have been made to depend, directly or indirectly, from a single independent claim 13, which was allowed in an earlier Office Action. The only amendments made to allowed claim 13 by the present amendment incorporate limitations from previously presented claims 8, 9 and 12. These claims are directed to specific antigens. Claims 8, 9 and 12 were rejected only over Collier et al. discussed below, as applied to now canceled claim 1. Claims 8, 9 and 12 were not rejected or objected to for any reason other than their dependency from claim 1. Claim 13 should therefore remain allowed. The amendments made herein do not contravene the earlier restriction requirement, because the previously examined claims were directed to species associated with pathogenic microorganisms (See Office Action dated 2/21/2003, p. 2).

For the convenience of the Examiner, the Detailed Action of the 3/25/2004 Office Action is set forth in the same order as presented in that paper.

Allowable Subject Matter

Applicants note with appreciation the allowance of claims 13 and 20.

Rejections Maintained

1. Rejection of Claims 3-4 under 35 USC 102(e) over Curtiss III, et al.

The independent claims subject to this rejection are claim(s): 3 –Now cancelled.

The Examine noted "that the features upon which applicant relies, (i.e. "**live bacteria with an altered Dam gene**) are not recited in the rejected claim(s) 3 and 4" (emphasis in original). Curtiss III et al., at certain cited portions, was said to "teach the importance of safe immunogenic compositions, which evidence enhanced and improved immunogenicity and safety, as live attenuated strains of bacteria with altered Dam activity. The reference inherently anticipates the instantly claimed invention of claims 3-4." The combination of claims 3 and 4 assertedly "defines a **phenotype** of altered activity that does not require the genotype to be a mutation in the Dam gene." (emphasis in the original).

Response

As pointed out previously, Curtiss III et al. 6,383,496 is only prior art insofar as it discloses subject matter in priority application 08/970,789, filed Nov. 14, 1997, now Patent 6,024,961 ("'961").

The '961 patent discloses recombinant avirulent immunogenic *Salmonella typhi* having a Ppos+ phenotype. The '961 patent teaches the selection or creation of Salmonella strains with a functional rpoS+ gene which produces a functional rpoS gene product. These strains are avirulent by virtue of their containing an attenuating mutation in one or more genes that renders the microorganism avirulent. In a preferred embodiment, the strains have at least two mutations each of which serves to attenuate the microorganism. A list of such mutation is found at Col. 8, ll. 58-60. This list does not include the *dam* gene.

Thus Curtiss III et al. does not meet the limitations of claim 13, including the requirement that the composition comprise an attenuated form of a live bacteria wherein the Dam activity is altered by a mutation in the *dam* gene.

The present claims are therefore allowable over Curtiss III et al.

2. Rejection of Claims 1-4, 7-9 and 12 under 35 USC 102(b) over Collier et al.

The Final Office Action maintained that Collier et al. teaches "strains of E. coli bacteria that evidence altered Dam activity. The carrier has not been so claimed to exclude the carrier/compositions of Collier et al., nor have the attenuated strains of Collier et al. that evidence altered Dam activity been shown to structurally differ from that which is claimed." The broth and antibiotics of Collier et al. are regarded as a "carrier." Further, applicants were said not to have shown that the compositions of Collier et al. are *not* immunogenic. These compositions were said to inherently meet the structural and functional limitations of the instantly claimed invention.

Response

The independent claims subject to this rejection are claim(s): 1 – which has been canceled.

Collier et al disclose, "a method for cloning genes that encode restriction endonucleases by altering the level of a methyl donor co-factor of a DNA methyltransferase that protects the DNA of a host cell from damage by a restriction endonuclease." (Abstract). In Example 3, the construction of a dam- E. coli strain that expresses beta galactosidase in response to DNA damage is described. A *dam*- derivative of a well known E. coli MC 1061 was used. The construct contained a dinD promoter controlling the expression of beta galactosidase, so that beta galactosidase was expresses in response to SOS-inducible DNA damage by a restriction endonuclease.

The "components" of Collier et al. are simply the growth media used for the various constructs, such as 2YT broth. Collier et al. does not teach a "pharmaceutically acceptable excipient" as recited in claim 13.

Furthermore, claim 13 recites certain heterologous antigens not taught or suggested by Collier et al. There is no discussion in this reference of specific antigens that may be

incorporated into the recited **immonogenic composition**. Thus, it is submitted that claim 13, as currently amended, and those claims dependent thereon are presently allowable.

3. Apparent rejection of clams 1 and 7 under 35 USC 102(b) over Anderson et al.

At paragraph 13 of the 3/25/04 Office Action it appears that a rejection over Anderson et al. is maintained from an earlier Office Action. The Office Action states that "Anderson et al. clearly teaches the utilization of dam mutant strains that evidence decreased Dam activity, to include dam negative strains (see Bale et al. abstract)." Anderson et al. is also said to incorporate by reference dam mutant strains, and to disclose a carrier.

Response

Anderson et al. teaches the use of E. coli hosts which have *dam* mutations. These hosts carry expression vectors for expressing improved quantities of a desired protein, e.g. chymosin. There is no disclosure concerning the preparation of these bacteria in excipients for administration, nor of the virulence of the hosts. There is further no disclosure of specific antigens encoded by a heterologous nucleotide sequence.

Thus, it is submitted that claim 13, as currently amended, and those claims dependent thereon should be allowable over Anderson et al..

4. Rejection of Claims 1 and 7 under 35 USC 102(a) over WO/98/12206 Shapiro et al.

Shapiro et al. is cited as disclosing a DNA adenine methyltransferase, which is a species of DNA adenine methylase. It was the Examiner's position that the claimed invention has not been structurally distinguished from Shapiro. Shapiro further discloses a glycerol stock, glycerol being a known pharmaceutical carrier.

Response

The independent claims subject to this rejection are claim(s): 3 – which has been cancelled.

Shapiro et al. discloses the isolation of a novel class of methyltransferase genes which are homologs of the bacterial *ccrM* gene. The ccrM protein is essential for viability (See p. 1, l. 25, and the article by Kahng et al., J. Bacteriol. 183:3065-3075 (2001, previously provided to the Office.) Therefore, a mutation in the *ccrM* gene, which is not taught by Shapiro et al., would not result in **live** attenuated bacteria, as recited in claim 13.

Furthermore, Shapiro et al. do not disclose or suggest the administration of bacteria containing an altered Dam gene, nor do they contemplate the use of any excipients. A pharmaceutically acceptable excipient is a relatively inert substance that facilitates administration of a pharmacologically effective substance. Examples are wetting agents, salts, encapsulating agents, etc. See specification p. 39, paragraph 00152. These are different materials than growth media.

Thus, it is submitted that claim 13, as currently amended, and those claims dependent thereon, are presently allowable.

Conclusion

It is believed that the present Amendments place the application in condition for allowance. Allowance of claims 2, 4, 7, 13 and 20 is respectfully requested. Such action, as well as the timely issuance of a Notice of Allowance is earnestly solicited. If a telephone conference would be useful in this case, the Examiner is encouraged to call the undersigned

at the number below to discuss any prosecution issues.

Respectfully submitted,

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